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EXAMINER	
SUGARMAN, SCOTT J	
ART UNIT	**PAPER NUMBER**
2873	

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Please find below and/or attached an Office communication concerning this application or proceeding.

SUPPLEMENTAL Notice of Allowability	Application No. 10/035,461	Applicant(s) CRUCE ET AL.	
	Examiner Scott J. Sugarman	Art Unit 2873	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. ~~If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course.~~ **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☐ This communication is responsive to _____.

2. ☒ The allowed claim(s) is/are *1-25*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

DETAILED ACTION

Reissue Applications

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. The specification and claims have been amended to comply with the format required under 37 CFR 1.173 as follows:

IN THE SPECIFICATION:

The specification is amended with the selected replacement paragraphs on the following pages.

Paragraph at c. 2, l. 37-54.

In practice, we typically probe many different types of molecules at once with the excitation light pulse. FIG.2 illustrates the case where a single short excitation pulse of light 30 is absorbed by a sample of identical molecules all at once. The fluorescence decay curve 32 resulting from a typical fluorescence response of a sample of identical molecules is exponential in nature because not all of the identical molecules emits its fluorescence photon at precisely the same time. The exponential decay follows a mathematical function so that we can calculate the fluorescence lifetime, τ:

$$[I(t) = I_0 \bullet e^{-(t-5_0)/\tau}]$$

$$I(t) = I_0 \bullet e^{-(t-t_0)/\tau}$$

where t_0 is the time of the excitation pulse, I_0 is the initial fluorescence and I(t) is the observed fluorescence intensity as a function of time.

Paragraph at col. 5, lines 30-43:

FIG. 5 is a block diagram of the generator component 54 of the present invention for generating the excitation signal. The present invention uses heterodyning techniques to produce two sinusoidal RF signals, a driving/reference signal 90 and a mixing signal 92. The present invention modulates the frequency of the two signals from 10 MHz to 200 MHz. One skilled in the art will appreciate that the present invention could vary the signals over a much larger frequency range. The preferred embodiment of the present invention generates the two signals with a frequency difference of 10 kHz. Another embodiment of the present invention generates the two signals using an adjustable offset frequency where the offset frequency is set through [to] the present invention's control software.

Paragraph at c. 11, l. 26-44.

Another, equivalent, way of writing the eigenfunction equations proceeds from the observation that:

$$\mathbf{G}\cdot\mathbf{A}^{-1}=\mathbf{cc} \tag{23}$$

and

$$\mathbf{S}=\mathbf{cs}\cdot\mathbf{A}=\boldsymbol{w}\cdot\mathbf{cc}\cdot\mathbf{T}\cdot\mathbf{A} \tag{24}$$

so that

$$\boldsymbol{w}^{-1}\cdot\mathbf{S}\cdot\mathbf{A}^{-1}=\mathbf{cc}\cdot\mathbf{T}=\mathbf{G}\cdot\mathbf{A}^{-1}\cdot\mathbf{T} \tag{25}$$

or

$$[\mathbf{G}^{-1}\cdot\boldsymbol{w}^{-1}\mathbf{S}\cdot\mathbf{A}^{-1}=\mathbf{A}^{-1}\cdot\mathbf{T}]$$

$$\underline{\mathbf{G}^{-1}\cdot\boldsymbol{w}^{-1}\cdot\mathbf{S}\cdot\mathbf{A}^{-1}=\mathbf{A}^{-1}\cdot\mathbf{T}} \tag{26}$$

Paragraph at c. 13, l. 10-40.

We may interpret the first of Eqns. (36) in terms of its column vectors as the representation of the r vectors of **cc** in the orthonormal basis of the r vectors of **U**:

$$\underline{c}_j = \sum_{i=1}^{r} \underline{U}_i P_{ij} \qquad (37)$$

where $[c_j]$ $\underline{c}_j$ is the jth column of **cc**, $[U_i]$ $\underline{U}_i$ is the ith column of **U** and P_{ij} is the corresponding element of $\mathbf{P_U}$. From this expression and the linear independence of the $[c_j]$ $\underline{c}_j$ and $[U_j]$ $\underline{U}_j$, we see that $\mathbf{P_U}$ is invertible. Linear independence of the $[c_j]$ $\underline{c}_j$ requires that:

$$\sum_{j=1}^{r} \alpha_j \underline{c}_j = 0 \qquad \text{only if} \qquad \alpha_j = 0 \qquad \text{for all } j=1,\ldots,r. \qquad (38)$$

From Eqn. (36), we see that Eqn. (37) implies:

$$\sum_{i,j=1}^{r} \underline{U}_i P_{ij} \alpha_j = 0 \ .$$

From the linear independence of the $[U_i]$ $\underline{U}_j$, we must have

$$\sum_{j=1}^{r} P_{ij} \alpha_j = 0, \qquad \text{for all } i = 1,\ldots,r. \qquad (39)$$

Paragraph at c. 14, l. 1-12.

A second method for solving Eqns. (30) is to use Eqn. (31) to write the pseudo inverse of **G**:

$$\mathbf{Gpi} = \mathbf{V} \cdot \mathbf{C}_1^{-1} \cdot \mathbf{U}^T \qquad (43)$$

so that we have:

$$\mathbf{G} \cdot \mathbf{Gpi} = \mathbf{U} \cdot \mathbf{U}^T \qquad \text{and} \qquad \mathbf{Gpi} \cdot \mathbf{G} = \mathbf{V} \cdot \mathbf{V}^T,$$

where $\mathbf{U} \cdot \mathbf{U}^T$ is [and] an NxN matrix and $\mathbf{V} \cdot \mathbf{V}^T$ is an MxM matrix, and each of these matrices is of rank r.

Equation 63, c. 15, l. 64.

$$[\eta = Tr(\mathbf{M}_V \cdot \mathbf{U} \cdot \mathbf{U}_T)]$$

$$\underline{\eta = Tr(\mathbf{M}_V \cdot \mathbf{U} \cdot \mathbf{U}^T)} \qquad (63)$$

Paragraph at c. 17, l. 1-6.

As the frequencies in ***w*** are large, we renormalize $\|w^{-1} \cdot Sx\|$ to equal $\|Gx\|$ so as to avoid skewing the results in favor of the **Gx** data 138. This amounts to a [resealing] rescaling of the units for the frequencies and the lifetimes. This [resealing] rescaling of units is compensated once the lifetimes are found, so they are expressed in seconds.

Paragraph at c. 18, l. 63 to c. 19, l. 16.

FIG.10 illustrates the present invention's ability to identify and discriminate between individual overlapping spectral components in a target mixture. The present invention allows for the extraction of both the individual fluorescence spectra and lifetimes from a target mixture of fluorophores. FIG.10 illustrates the present inventions ability to differentiate spectra using a three-dye mixture of OXAZINE™ 720, 725 and 750. OXAZINE is a trademark of Excition, Inc. We mixed the dyes at equal concentrations of 3.3 μM. We recorded the emission spectra for an excitation signal wavelength of 640 nm and the laser modulation frequency was swept (modulated) from 10 MHz to 140 MHz at 5 MHz increments. The present invention extracted fluorescence lifetimes of 3.705 nsec for Oxazine 720 (196 on FIG.10), 1.979 nsec for Oxazine 750 [(] (198 on FIG.10), and 0.5588 nsec for Oxazine 725 (200 on FIG.10). The results from the present invention compared very well with the listed individual dye fluorescence lifetimes of 3.739 nsec for Oxazine 720, 2.014 nsec for Oxazine 750 and 0.9935 nsec for Oxazine 725. The individual spectra extracted for each dye from the mixture revealed spectral characteristics that matched with spectra obtained from the individual dyes.

IN THE CLAIMS:

1. (Thrice Amended) An apparatus for fluorescence lifetime and spectral measurements, comprising:

a driving/reference signal generator that generates a driving/reference signal, said driving/reference signal is amplitude and/or frequency modulated over time;

a mixing signal generator that generates a mixing signal, said mixing signal is amplitude and/or frequency modulated over time;

an excitation signal generator that generates an excitation signal, the driving/reference signal drives said excitation signal generator;

a signal detector that detects the emitted signal;

a mixer that mixes the [emitted] mixing signal with the driving/reference signal and produces the processor reference signal;

a mixer that mixes the emitted signal with the mixing signal and produces the data signal; and

a processor that extracts the fluorescence lifetime and fluorescence spectrum of the emitted signal from the comparison of the processor reference signal with the data signal using a chemometric analysis.

6. (Thrice Amended) A system for fluorescence lifetime and spectral measurements, comprising:

means for generating [the] a driving/reference signal, said driving/reference signal means modulates the amplitude and/or the frequency of the driving/reference signal over time;

means for generating a mixing signal, said mixing signal means modulates the amplitude and/or the frequency of the mixing signal over time,

means for generating an excitation signal, the driving/reference signal drives said excitation signal means;

means for detecting the emitted signal;

means for mixing the [emitted] mixing signal with the driving/reference signal to produce the processor reference signal;

means for mixing the emitted signal with the mixing signal to produce the data signal; and

a processor that extracts the fluorescence lifetime and fluorescence spectrum of the emitted signal from the comparison of the processor reference signal with the data signal using a chemometric analysis.

11. (Twice Amended) A method for measuring the fluorescence lifetime and the fluorescence spectrum, comprising the following steps:

generating a driving/reference signal and modulating the amplitude and/or the frequency of the driving/reference signal over time;

generating a mixing signal and modulating the amplitude and/or the frequency of the mixing signal over time;

generating an excitation signal from the driving/reference signal;

detecting the emitted signal,

mixing the [emitted] mixing signal with the driving/reference signal and producing the processor reference signal;

mixing the emitted signal with the mixing signal producing the data signal; and

extracting the fluorescence lifetime and fluorescence spectrum of the emitted signal from the comparison of the processor reference signal with the data signal to measure using a chemometric analysis.

16. (Thrice Amended) A method of producing an apparatus for fluorescence lifetime and spectral measurements, comprising:

providing a driving/reference signal generator that generates a driving/reference signal, said driving/reference signal is amplitude and/or frequency modulated over time;

providing a mixing signal generator that generates a mixing signal, said mixing signal is amplitude and/or frequency modulated over time;

coupling an excitation signal generator that generates an excitation signal and a reference signal to said driving/reference generator;

providing a signal detector that detects the emitted signal;

coupling a first mixer to said excitation signal generator, said mixer mixes the [emitted] mixing signal with the driving/reference signal to produce the processor reference signal,

coupling a second mixer to said mixing signal generator, said mixer mixes the emitted signal with the mixing signal to produce the data signal; and

coupling a processor to said first mixer and said second mixer, said processor extracts the fluorescence lifetime and fluorescence spectrum of the emitted signal from the comparison of the processor reference signal with the data signal using a chemometric analysis.

21. (Thrice Amended) A program storage device readable by a computer, tangibly embodying a program of instructions executable by the computer to perform method steps for a method for measuring the fluorescence lifetime and the fluorescence spectrum, comprising the following method steps:

generating a driving/reference signal and modulating the amplitude and/or the frequency of the driving/reference signal over time;

generating a mixing signal and modulating the amplitude and/or the frequency of the mixing signal over time;

generating an excitation signal from the driving/reference signal;

detecting the emitted signal;

mixing the [emitted] mixing signal with the driving/reference signal and producing the processor reference signal;

mixing the emitted signal with the mixing signal producing the data signal; and

extracting the fluorescence lifetime and fluorescence spectrum of the emitted signal from the comparison of the processor reference signal with the data signal to measure using a chemometric analysis.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott J. Sugarman whose telephone number is (571)272-2340.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ricky L. Mack can be reached on (571)272-2333. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott J. Sugarman
Primary Examiner
Art Unit 2873

sjs
May 15, 2006